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Alexandria, VA 22313-1450

Declaration of Inventor Ronald Aung-Din, M.D.

I, Dr. Ronald Aung-Din, a citizen of the United States and resident of the state of Florida, U.S.A., declare and state as follows:

1. I am the named inventor of the above-referenced patent application. I am also President of AfGin Pharma LLC, the assignee of the above-referenced patent application.

2. My educational background is as follows: I have a B.S. in Mechanical Engineering from Bucknell University, Lewisburg, PA; an M.S. in Environmental Engineering from Cornell University, Ithaca, NY; an M.S. in Pre-Med and Biochemistry from Columbia University Institute of Human Nutrition, New York, NY; an M.D. from Southwestern Medical School, University of Texas Health Science Center, Dallas, TX (with a Cardiology Student Fellowship at Oxford University, Oxford, England); Neurology and Neurosurgery Residency, University of Florida, Gainesville, FL. with a Post-Doctoral Fellowship in

Clinical Neurology at the National Hospital for Neurological Disease in London, England. Residency, University of Florida, Gainesville, FL. with a Post-Doctoral Fellowship in Clinical Neurology at the National Hospital for Neurological Disease in London, England.

3. During my Neurosurgery Residency, I also successfully completed a special course in micro-neurosurgery with particular attention to the brainstem and posterior fossa structures.

4. Added to my 8 years of Neurology and Neurosurgery Residency training, I have over 24 years of experience in my private practice of General Neurology and Neuropsychiatry in Sarasota, Florida. Additionally, I have acted as Principal Neurological Investigator in over 20 Clinical Trials sponsored by the pharmaceutical industry over the past 6 years as a Research Neurologist.

5. In this Declaration, I will discuss experimental evidence that shows that the application of the claimed topical formulation of an indole serotonin agonist (e.g., triptans) at the back of the neck at the hairline provides significantly more rapid and complete treatment of migraine or cluster headache than at other areas of the skin on the human body. The summary of my work provided below led me to conclude that Topical Regional Neuro-Affective ("TRNA") is indeed revolutionary, invoking a novel delivery of the serotonin agonist class of triptans, not previously described or used in human subjects.

6. My decision to look into an alternate delivery of the triptans came out of a necessity I observed in my patients using traditional triptans. In summary, there were issues with delay of clinical benefit with the oral triptans, the significant "triptan effects" with the subcutaneous injection, the unacceptable taste associated with the nasal spray; not to mention problems with gastro-intestinal transit delay and hepatic first-pass metabolism. Furthermore, it seemed targeted delivery more closely applied to the area of pathology---the brain, in particular, the Cervico-Trigeminal Complex (the "Migraine Generator), seemed more appropriate than

having drug delivered all over the body, reaching the intended areas only as a consequence of general systemic delivery through blood flow.

7. I initially applied the compounded (in a suitable dermal penetration-enhancing medium) topical sumatriptan cream to the forehead and the fronto-temporal regions as these were areas head pain in migraine was most significantly experienced by patients. Later, with closer evaluation of the anatomical basis of migraine---that pain in the fronto-temporal area, the frontal sinus region, the occipital area, and neck, are all reflections of involvement of the Cervico-Trigeminal Complex and its areas of innervation with "referred" pain to these areas (see reference #5 by Piovesan, et al., and reference # 6 by Bartsch, et al. in my article in *Drug Delivery Technology*, October 2009 (at page 44), attached as Exhibits A, B, and C to my Declaration, respectively; and (Bogduk, Cervicogenic Headache: Anatomic Basis and Pathophysiologic Mechanisms, Current Pain and Headache Reports 2001, 5:382 (Exhibit D)), I experimented with applying the compounded cream at the back of the neck at the hairline ("BONATH") of patients suffering from acute migraine.

Application to the Forehead/Fronto-Temporal Region

8. The efficacy of topical sumatriptan was studied over a six week period in 22 migraineurs who had currently been treated with injectable, nasal spray or oral sumatriptan.

9. Commercially available sumatriptan tablets were crushed and compounded in Lipoderm® in a concentration of 100 mg/ml. Patients were instructed to apply 50 mg of sumatriptan to a clean area of the forehead on the side of the headache at a time they would usually resort to using sumatriptan for relief. An additional 50 mg dose could be applied after 1 hour if the first dose was ineffective.

10. Further details of this study are found in the specification of my patent application at Examples 1 and 3, and in my Abstract published in *Cephalalgia*, 2001, p 412 (attached as Exhibit E to this Declaration).

Application at the Back of the Neck at the Hairline ("BONATH")

11. Over a six week period, 42 patients with acute moderate-to-severe migraine were treated with 12.5 mg of extracted sumatriptan in Lipoderm®. The transdermal sumatriptan formulation was applied to the mid-posterior cervical area at the hairline using a calibrated 1 cc syringe (0.1 ml of 125 mg/ml).

12. Further details of this study are found in my Abstract published in *Headache*, 2003, Volume 43, #5, p. 523 (attached as Exhibit F to this Declaration). This study is also (partially) reported in the specification of my patent application at Examples 7 and 8.

Results

13. A comparison of the results of the two studies discussed briefly above are provided below:

	Year	#pts.	Dose*	% relief/response**	time to relief/response
Forehead:	**2001**	**22**	**50-100mg**	**55%/36%**	**9% by 10min. 18% by 30min. 27% by 1 hr. (response times not measured)**
"BONATH":	**2003**	**42**	**12.5mg**	**100%/95%**	**84% by 5min./32% at 10 min. 98% by 10min./93% at 30 min.**

100% by 15min./95% at 1 hr.

*** dose of compounded sumatriptan**

****Relief**: when head pain and migraine symptoms are first noted to be alleviated.

****Response**: when severe-to-moderately severe pain and symptoms are relieved to the point of mild-to-none.

14. In view of the results obtained, it is my opinion that in a comparison of compounded sumatriptan (Imitrex®) topical application at the forehead and at the back of the neck at the hairline ("BONATH") as abortive therapy during acute migraine, the unique nature of the "BONATH" anatomical site for topical regional neuro-affective ("TRNA") therapy, showed that application of the immediate release topical triptan formulation in significantly lower drug doses provided faster relief and response times, and significantly more complete relief.

<u>Topical Application Elsewhere</u>

15. In the several instances where compounded sumatriptan cream had been applied elsewhere on the body---for example, the hand, no clinical effect was noted.

<u>Unexpected Results</u>

16. Unexpectedly (and to my surprise), I found migraine pain and symptom relief to be significantly more rapid, in addition to being more complete at the "BONATH" than at the other areas I had previously used---the frontal and temporal regions.

17. This finding was so dramatic in nature it was specifically expressed and documented in a video-tape of two treated patients made in May of 2001. The tape, together with my first poster on the subject, was presented in June 2001 in New York City at the International Headache Congress. My patients were also

henceforth instructed to only apply the compounded sumatriptan to the back of the neck at the hairline, "BONATH".

18. Through my prior extensive experience with traditional triptan deliveries (injection, oral, and nasal spray), I realized the significantly more rapid onset of head (and neck) pain and migraine symptom relief could not be explained by active drug absorption into the blood with eventual delivery through the circulatory system to the sites of migraine pathology. Observations with TRNA in established migraineurs with prior traditional triptan use indicated onset of relief of headache and other migraine symptoms occurred in the majority within 10 minutes of topical sumatriptan application. Headache response (moderate/severe to mild/none) was achieved in the majority within 30 minutes; less than 10 minutes in 30%. These sorts of responses had not been reported with the sumatriptan tablet and nasal spray. To my experience, these responses at BONATH application were even superior to the subcutaneous sumatriptan injection. The dose of topical triptan (sumatriptan/Imitrex®) was also significantly less than usual oral dose---12.5 mg topical vs. 100 mg oral.

19. Furthermore, none of the usual side-effects of traditional therapy (the result of active drug in the systemic blood) were encountered with TRNA; these being the "triptan effects" of chest tightness, tingling of the face and extremities, fatigue, and lethargy. The relatively high "therapeutic" blood drug levels of triptan required with traditional triptan delivery for clinical effect at the target sites are responsible for these commonly encountered side effects. These triptan side-effects are particularly more significant with the subcutaneous sumatriptan injection as the result of the "bolus effect" of high drug blood levels of sumatriptan.

20. It became apparent there had to be another explanation for the results I was observing as they were distinctly different from what I had encountered with triptan therapy in the past. I believe the results may be in part explained by the fact that the forehead and BONATH are both innervated by the Trigeminal System with cutaneous free nerve-endings leading back to trigeminal nuclei

except that, at the BONATH: 1.) both sides of the Trigemino-Cervical Complex are activated, 2.) a greater concentration of cutaneous free nerve-endings with afferent input exist (C1-C4), 3.) there is closer proximity to the Migraine Generator within the cervical cord and brainstem, and 4.) there is contributory afferent neural input by the Vagus and Cervical Sympathetic Nerves in the neck.

Systemic Triptan Drug Delivery

21. Systemic triptan drug delivery using blood flow and requiring "therapeutic" blood drug levels, by either patch, subcutaneous injection, or topically, must first enter the venous system of the subcutaneous tissue via venules (small veins) and be transported by the venous system to the heart before reaching the brain. The body's arterial system transports drug to the areas of migraine pathology within the brain---the Trigemino-Cervical Complex and its areas of innervation. The Vertebro-Basilar System (Posterior Circulation of the Brain) at the back of the head and neck is the primary blood supply to the Trigeminal Nerve System. Accordingly, drug delivered using the skin in this manner would not be conducive for use as "acute" abortive treatment for a migraine attack. Time from application to the skin to clinical benefit would be relatively long and unacceptable to patients---likely much greater than 30 minutes; and more likely, an hour or more, for significant clinical effect.

22. If the observed clinical benefit of TRNA is on the basis of absorption into the blood (via a transdermal patch as described in U.S. Patent No. 5,807,571 (List) and as presently contemplated for commercialization by NuPathe, Inc. as the Zelrix™ iontophoretic patch), active drug would have to enter the arterial capillaries or venules in the skin and soft tissue, before transport by the venous system to the heart and eventual delivery to the brain in the manner described above.

23. The Vertebro-Basilar arterial circulation cannot be directly accessed by drug in the small vessels of the forehead, scalp, or back of the head or neck as these

vessels of necessity must first flow back to the heart via the systemic venous system; it is only accessed by the arterial blood from the heart going to the brain by the vertebral arteries. To suggest otherwise is counter to the physiologic flow of blood as we know it. Active drug that has entered the small veins (venules) in the skin (subcutaneous tissue) through a concentration gradient mechanism, must flow back through progressively larger and larger veins, eventually ending as the vena cava emptying into the heart. Likewise, the small arterial vessels in the skin and subcutaneous tissue are the end branches of arterioles and arteries of the systemic arterial system flowing from the heart. Accordingly, any drug/triptan that could have entered the small arterial vessels in the skin cannot flow back directly to the vertebro-basilar arterial system to affect the Trigemino-Cervical Complex with its anti-migraine effects as it is counter the normal direction of arterial blood flow---which is from larger to smaller vessels, ending with capillaries in the skin and end-organs. With the venous system, it is opposite---from smaller to progressively larger vessels with eventual end at the heart.

BONATH Administration

24. The above finding with resultant further evaluation of the anatomical site at the BONATH, lead me to conclude that there are no other areas in the human anatomy where cutaneous free nerve-endings are capable of providing such a concentrated degree of afferent neural feed-back to the Cervico-Trigeminal Complex within the cervical spinal cord (Nucleus Caudalis) and the brainstem (Nucleus Proper of the Trigeminal Nerve).

25. Further, as alluded to above, not only was afferent input provided by the Trigeminal System, but also, by the Vagus Nerve and the Cervical Sympathetic Nervous System through their connections with cervical nerves within the soft tissues of the neck. The Vagus Nerve provides the greatest amount of afferent input to the brain from the rest of the body. In addition to the Trigeminal system, upper cervical nerve roots have afferent connections with the vagus nerve and the sympathetic system through the sympathetic ganglia. The vagus nerve includes

both efferent and afferent fibers and is attached to the lower brainstem (medulla oblongata) via 8-10 radicles. The vagal afferent fibers arise in the jugular and the nodose vagus ganglia. The vagal somatic afferent fibers terminate in the nucleus of the trigemino-spinal tract. Both the jugular and the nodose ganglia are connected with the superior cervical sympathetic ganglion through inter-communicating rami. The superior cervical sympathetic ganglion is located between the internal carotid artery and the jugular vein on the ventral aspects of the transverse processes of the 2nd , 3rd , and the 4th cervical (C2-C4) vertebrae. It is the largest of the sympathetic trunk ganglia. Sympathetic roots arising from the ganglion join the 1st and the 2nd cervical nerves; frequently the 3rd , and occasionally, the 4th: C1-C4. In addition to nerve fibers which extend rostrally to the CNS from the superior cervical sympathetic ganglion, the sympathetic innervation of the head includes fibers which join the neural plexi on the common carotid and the vertebral arteries.

26. From the above, it is clear that upper cervical (C1-C4) nerve function with peripheral nerve free nerve- endings in the skin at the back of the neck (BONATH) is intimately related to vagus nerve afferents, afferents from the face, head, and the dura of cranial fossae through the trigeminal nerve, and those from the sympathetic system. These provide feedback to the brainstem and other CNS structures for nerve signal processing and modulating efferent output.

27. The Trigeminal nerve specifically provides innervation to C1-C4 at the back of the neck as the "cervical" component of its Cervico-Trigeminal Complex. Accordingly, topical delivery of triptan as described by TRNA would be ineffective at any other place on the body except at BONATH. There do not exist the neural connections between the Trigeminal System with free nerve-endings of the skin as at BONATH. This situation, together with the additional afferent input from the Vagus Nerve and the Cervical Sympathetic Nervous System makes BONATH unique, having a situation existing nowhere else in the human anatomy with respect to the possibility for topical regional neuro-affective (TRNA) therapy.

28. Thus, in my opinion the results observed by TRNA can only be explained by "neuro-affective" effects. The active drug effect in TRNA appears to be at the free nerve-ending receptor sites. Drug appears not to be "absorbed" by the nerves or taken up; drug appears to act at the neuro-transmitter receptor sites on the free nerve-endings, the effect of which is then transmitted by neural impulse propagation as afferent input to the cervical spinal cord, brainstem, and other CNS structures where clinical effect and benefit is realized. Thus, the mechanism is electro-chemical in nature---how the nervous system operates: neurochemical interaction between the pre- and post-synaptic neurons across the synapse which results in an electrical (neural) impulse.

29. With drug delivery using the circulatory system (I.V. injection, transdermal patch, patch with "spikes", oral) active drug at a "therapeutic level" must be achieved and delivered to the neural structures involved with the pathological process by the blood. With this process, the analogy is that of filling a reservoir using the principles of fluid dynamics with all the factors that influence it: cardiac/pump function, vascular disease, blood volume, etc.

30. With TRNA, the analogy is of an electrical capacitor which sends an electrical impulse after a certain charge build-up. As such, it is not influenced by blood flow factors or drug blood levels. It is only influenced by local drug concentration and its specific neuro-transmitter function characteristics at the free nerve-ending receptors---located just below the stratum corneum of the skin.

31. In contrast, with transdermal patch delivery, active drug is required to traverse the full extent of the skin to enter blood vessels within the sub-cutaneous tissue, a relatively greater distance in comparison to the free nerve-ending level below the skin surface. Such is the reason the NuPathe transdermal sumatriptan patch requires an electrical iontophoretic current to enhance entry of active drug into the small subcutaneous blood vessels. It is reported by NuPathe that "therapeutic blood levels" of triptan are maintained for long periods of time with the patch. These can be a source of prolonged triptan-related systemic side-effects, of which

there are already significant complaints among triptan users. Because of these and the other factors described above, the transdermal sumatriptan patch is not conducive for use as "acute abortive" therapy for migraine. In contrast, the clinical results with TRNA sumatriptan compounded cream at "BONATH" suggest it is excellent as a triptan delivery process for the abortive treatment of migraine. Recall that with the subcutaneous sumatriptan injection, high blood levels of sumatriptan are achieved relatively quickly such that this delivery method may be considered acute abortive migraine therapy. However, the downside is the associated increase in "triptan side-effects" from the drug bolus effect as well a rapid "wash-out" with potential for recurrence of migraine symptoms as drug blood levels quickly fall.

32. In summary, the proposed "neuro-affective" mechanism for TRNA triptan delivery arose out of the need to explain several observations which were contrary to previous experience (both personal and reported in literature) with "systemic" triptan delivery requiring "therapeutic" levels of drug in the blood: 1.) The onset of migraine pain and symptom relief with TRNA sumatriptan rivaled; and, in some instances, was better than the subcutaneous injection, 2.) Migraine relief was more complete and without the recurrence noted with the injection, 3.) None of the "triptan effects" of the injection, related to the associated relatively high drug blood levels, were noted with TRNA sumatriptan therapy---the only mentioned side-effects with TRNA sumatriptan have been "a tingling in the skin" at the site of topical drug application and "a warm sensation" in the back of the neck. Accordingly, an explanation needed to be found for the observed triptan effect of migraine symptom relief that did not appear to involve blood flow and drug blood levels, which was associated with a rapid therapeutic benefit.

33. These apparent contrary findings led to a further investigation of the neuro-anatomy and neuro-physiology of the skin at the back of neck at the hairline, "BONATH". The discovery was of cutaneous free nerve-endings at this location having a unique relationship with the Trigeminal, Vagal, and Cervical

Sympathetic afferent nervous systems as outlined above, existing no where else, making it conducive to the TRNA delivery of triptans.

Enablement Rejection

34. I am advised that the Examiner has further rejected my patent application based on non-enablement of topical administration of other triptans besides sumatriptan. In this regard, I have also on a few occasions administered two other indole serotonin agonists, rizatriptan benzoate (derived from Maxalt®) and frovatriptan succinate (derived from Frova®) at doses of 1-2 mg and 0.5-1 mg respectively to migraineurs using the same aqueous based vehicle described in Examples 4 and 7 of my presently considered patent application. These administrations provided efficacy to these migraineurs.

Conclusion

35. I declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: Jan. 4, 2010.

Name: ____________________
Dr. Ronald Aung-Din

Exhibit A

Referred pain after painful stimulation of the greater occipital nerve in humans: evidence of convergence of cervical afferences on trigeminal nuclei

EJ Piovesan*, PA Kowacs, CE Tatsui, MC Lange, LC Ribas & LC Werneck

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Cephalalgia

Piovesan EJ, Kowaca PA, Tatsui CE, Lange MC, Ribas LC & Werneck LC. Referred pain after painful stimulation of the greater occipital nerve in humans: evidence of convergence of cervical afferences on trigeminal nuclei. Cephalalgia 2001; 21: 107–109. London. ISSN 0333-1024

Cranial sensory innervation is supplied mainly by the trigeminal nerves and by the first cervical nerves. Excitatory and inhibitory interactions among those nerve roots may occur in a mechanism called nociceptive convergence, leading to loss of somato-sensory spatial specificity. Three volunteers in an experimental trial had sterile water injected over their greater occipital nerve on one side of the neck. Pain intensity was evaluated 10, 30 and 120 s after the injection. Two of the patients reported intense pain. Trigeminal autonomic features, suggestive of parasympathetic activation, were seen associated with trigeminally distributed pain. These data add to and reinforce previous evidence of convergence of cervical afferents on the trigeminal sensory circuit. □ *Cervical spinal cord, occipital nerve block, pain*

Elcio Juliato Piovesan, Serviço de Neurologia, Hospital de Clínicas da UFPR, Rua General Carneiro 181, 12 (0) andar, Sala 1236 – ZIP 80060–900, Curitiba, Paraná, Brazil, e-mail piovesan@avalon.sul.com.br *Received 28 October 1999, accepted 19 January 2001*

Introduction

Cranial sensation is provided by afferents of the trigeminal nerve and the first cervical roots, intermingled in association or dissociation (1). However, convergence of pain has not been studied in detail in humans, since most descriptions refer to case reports in which this type of phenomenon is secondary to vascular or tumoral aetiology (2). For ethical reasons, some studies to clarify pain mechanisms in humans cannot be routinely carried out. This paper refers to a unique opportunity to study the projections of the greater occipital nerve (GON) through painful stimuli.

Patients and methods

Three of the patients presented here had already been studied in previous research (3). All the patients included had right side-locked migraine attacks. Injections over the GON were carried out transcutaneously according to the procedure described by Vital (4, 5), only on the right side. All patients received 2 ml of sterile water (SW) injected over the right GON. The intensity of the pain was evaluated through a visual analogue scale (VAS) (6), during and 10, 30 and 120 s after the injection. Pain was classified as low, moderate and severe, for VAS measurements ranging from 0 to 30 mm, 31–52 mm and greater than 52 mm, respectively (7). The patients also drew their sites of perceived pain on a sketch of the head (Fig. 1).

Results

Ten seconds after the injection, the patients developed severe pain at the site of injection. For patient No. 2, the pain was kept limited to her right GON territory, gradually subsiding. The other two patients had referred pain, projecting not only over their right GON territories but also over the areas innervated by the first branch of the trigeminal nerve (V_1) on the same side of the head.

Ten seconds after the injection, patient No. 1 suffered severe pain, involving not only the territory of the right

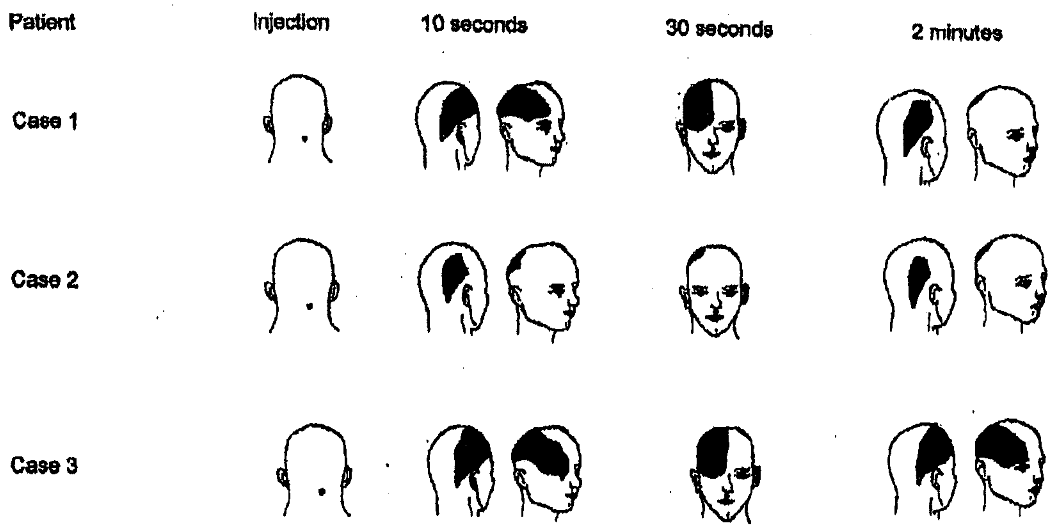

Figure 1 Distribution of the pain sensory symptoms.

Table 1 Pain distribution and intensity

Patient	Immediate	10s	30s	120s
1	Local	GON+V1	GON+V1	GON
(VAS)	3	7	10	4
2	Local	GON	GON	GON
(VAS)	4	10	9	4
3	Local	GON+V1	GON+V1	GON+V1
(VAS)	5	8	10	10

VAS, visual analogue scale; GON, greater occipital nerve; V1, first trigeminal branch; s, seconds.

GON but also her right supraorbital area. Those pains reached a severe, excruciating intensity 30 s after the injections. Two minutes after the injection the V_1 pain had subsided completely but the pain in the GON territory persisted, although moderate in intensity. Facial flushing, conjunctival injection and tearing on the same side of the head developed along with the pain and subsided after 1 min.

Patient No. 3, 10 s after the injection, had severe pain not only at his right GON, but also projecting to the territory of his right first trigeminal cutaneous innervation (v_1), including the eyeball. Thirty seconds after the injection the pain was excruciating in both territories and was maintained in both areas for 2 min. Five minutes after the injection the V_1 component subsided. Ipsilateral facial flushing, conjunctival injection and tearing also developed along with the pain and subsided after 60 s.

Patients 1 and 3 described their trigeminal pains as lancinating with intermingled paroxysms lasting approximately 2–3 s. For both it was perceived as more intense than the occipital pain. Right occipital pain lasted an average of 4 h and was the only pain in patient 2. Table 1 summarizes the distribution and evolution of the VAS scores of the three patients, from the infiltration until 2 min later.

Discussion

Cranial nociceptive volleys are perceived, processed and carried by highly specialized structures towards trigeminal nuclei cells in the pons, medulla oblongata and upper spinal cord (8). The trigeminal nuclei and the upper spinal cord posterior roots have a close anatomical and functional relationship, which leads to convergence of the posterior upper cervical roots on the nucleus trigeminalis caudalis and the dorsolateral nuclei of the upper cervical spinal cord (9, 10). Unilateral stimulation of the GON elicits pain in its territory and in areas innervated by other nerves, mainly in those pertaining to the ipsilateral first trigeminal branch (11–13). This convergence mechanism can be clinically appreciated in most forms of primary headache as in those headaches stimuli arising from the neck can trigger ipsilateral headaches projecting onto trigeminal territories (11). On the other hand, experimental studies on animals

have shown that mechanical (14) and electrical (15) stimulation of intracranial vascular structures, such as the middle cerebral artery (in rats), the superior sagital sinus (in rats and in the macaca nemestrina) (15), and of the anterior and posterior cranial cavities, activates cells in the nucleus trigeminalis caudalis and/or the dorsal horn down to the C2 level (16). Perhaps some clinical correlates of these projections are the pain secondary to middle cerebral artery dilatation, that projects to trigeminal areas where migraine pain is most often experienced (17), and the occipital and neck pain that may be observed during migraine and cluster headache attacks (18, 19).

The symptoms presented by the patients can be attributed to activation of the delta-A group fibres (type III fibres) as those fibres are characterized by rapid synaptic responses of second order neurones in the dorsal horn (19). The short-lasting, lancinating pain, emerging approximately 10 s after the sterile water injection, associated with autonomic symptoms on the same side, suggests not only convergence to V1 nuclei, but also parasympathetic and/or antidromic trigeminal vascular activation. This autonomic activation echoes the clinical findings of some cephalalgias with trigeminal autonomic features, such as cervicogenic headache, chronic paroxysmal hemicrania and SUNCT syndrome, in which unilateral trigeminal pain, associated with ipsilateral parasympathetic activation, can be triggered by neck movements (20).

Intracutaneous sterile water injections have been reported to relieve acute labour pain and cervical pain in whiplash patients (21), but in some cases of secondary headache the sterile water injection is not effective (22).

Our findings support the existence, in humans, of convergence of cervical nociceptive projections to the trigeminal nuclei. Its relevance for the physiology of cranial sensation, as well as its role in primary headaches, is not fully known. Whether GON afferences converge only on the nucleus trigeminalis caudalis or on higher levels remains to be clarified.

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Exhibit B

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Increased responses in trigeminocervical nociceptive neurons to cervical input after stimulation of the dura mater

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Pain referral and spread in headache patients may be attributed to a sensitization of central nociceptive neurons with an increased excitability to afferent input. We investigated if noxious dural stimulation evokes sensitization of second-order neurons that leads to an increased responsiveness to stimulation of cervical afferents. Recordings were made from 29 nociceptive neurons in the C_2 dorsal horn of the rat that received convergent synaptic input from trigeminal and cervical afferents. Trigeminal afferents of the supratentorial dura mater were activated by mustard oil (MO) and the responses of second-order neurons to stimulation of the greater occipital nerve (GON) were studied before and after dural stimulation. Projection sites to the contralateral thalamus were determined by antidromic stimulation. After dural application with MO, mechanical thresholds of the dura significantly decreased ($P < 0.05$) and an enlargement of the trigeminal and cervical cutaneous mechanoreceptive fields was observed in 71% of neurons. The responses to noxious mechanical

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stimulation of deep paraspinal muscles increased after MO application ($P < 0.001$). Similarly, an increase in the excitability to electrical stimulation of the GON was observed in C-fibre responses ($P < 0.001$). These results suggest that stimulation of nociceptive afferent C-fibres of the dura mater leads to a sensitization of second-order neurons receiving cervical input. This mechanism might be involved in the referral of pain from trigeminal to cervical structures and might contribute to the clinical phenomena of cervical hypersensitivity in migraine and cluster headache. Understanding this interaction is likely to be pivotal in characterizing the physiology of treatment with manipulations involving cervical input, such as GON injection.

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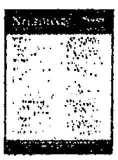

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Exhibit C

TOPICAL DELIVERY

Topical Regional Neuro-Affective (TRNA) Therapy: Novel Ground-Breaking Triptan Drug Delivery for Treating Migraines

By: Ronald Aung-Din, MD

INTRODUCTION

Current short-comings in triptan therapy for migraine may now be overcome by the concept of topical regional neuro-affective (TRNA) therapy. This novel, proprietary (European Patent No. 1 435 945, granted Febraury 2008) triptan delivery is unique in providing therapeutic benefit while avoiding both systemic and cerebral blood. Drug blood levels are unnecessary as therapeutic effect is achieved by direct serotonin agonist (triptan) action on unmyelinated cutaneous free nerve-endings below the skin surface (stratum corneum) at the back of the neck (Figures 1 and 2).[1]

There exist free nerve-endings in the skin at the upper posterior cervical region (the back of the neck at the hairline, BONATH) as components of peripheral nerves of the region. These comprise branches of cervical nerve roots, C1-C4, which constitute the tract and nucleus of the Spinal (Caudal) Nucleus of the Trigeminal Nerve System (TNS), the Migraine Generator responsible for the migraine process within the cervical cord and brainstem. Roughly estimated, there is in the order of hundreds of thousands to millions of free nerve-endings in the approximate 12- to 14-cm square area of this anatomy that feedback to the trigemino-cervical neural complex.[2-4]

MIGRAINE PATHOPHYSIOLOGY & NEUROANATOMY

To appreciate TRNA technology, review of migraine pathophysiology and the region's neuroanatomy is in order (Figure 3). Migraine is believed the result of neuronal hyperexcitability within TNS. TNS provides pain and sensory input from the face, head and neck, sinus cavities, and intracranial dura and vessels. Migraine may be triggered by disturbances within these peripheral TNS components with subsequent involvement of central structures, resulting in typical symptoms of an attack. Certain odors or irritants stimulating the sinuses, neck muscle tension, changes in barometric pressure, sleep loss, stress, and other triggers can precipitate migraine. As TNS and other CNS structures become involved, head pain, nausea, and light and noise sensitivity become prominent. Cutaneous allodynia or unpleasant sensations of the skin affecting the face, scalp, and back of the neck is an early indication of the start of migraine. These symptoms represent neural irritation at the cutaneous free nerve-ending level within peripheral components of TNS.[3-6]

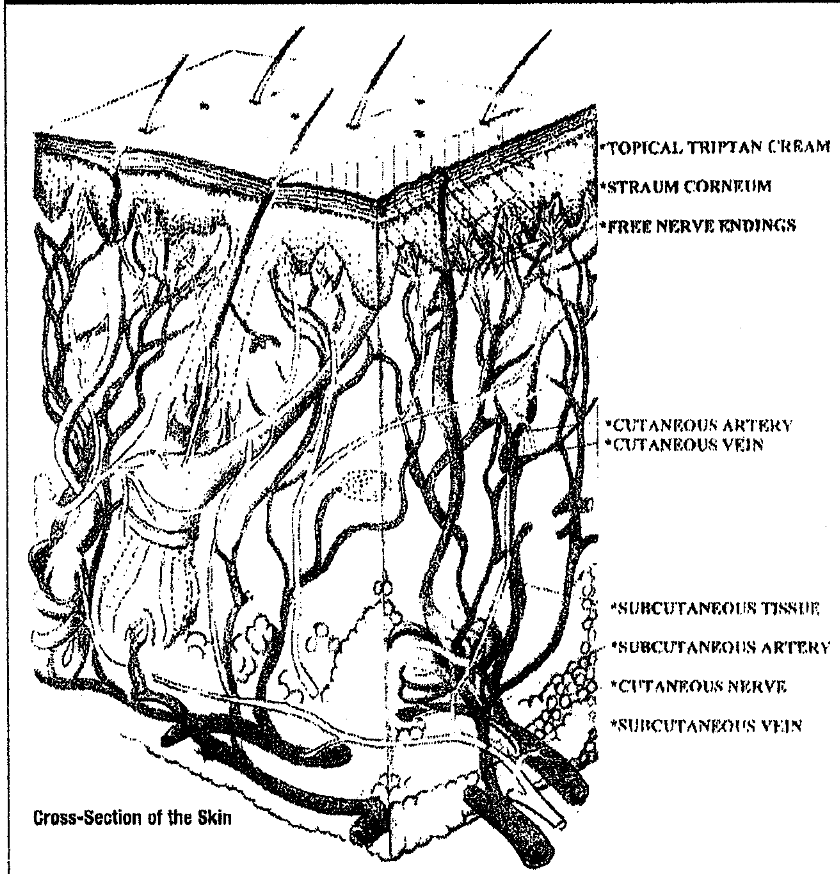
Triptans, as serotonin agonists, are thought to treat migraine symptoms by inhibiting neural transmission to central TNS structures and down-regulating neuronal hyperexcitability within TNS. Other events include dural vascular constriction with reduced permeability and diminished chemical inflammation. TRNA therapy allows expeditious triptan TNS down-regulation through direct peripheral afferent neural input from cutaneous free nerve-endings. This feedback down-regulation of CNS efferent neural output through peripheral afferent input activation is the same as in vagal nerve stimulation (VNS) for the treatment of seizures, headache, and depression. As CNS efferent activity is modulated, clinical symptoms of neuronal hyperexcitability as seizures or migraine are reduced.[7]

In addition to that by TNS, CNS afferent input from cutaneous free nerve-endings from BONATH is provided by the vagus nerve and the sympathetic nervous system through cervical neural connections within the soft tissues of the neck via vagal and sympathetic ganglia. The result is afferent neural input from skin at BONATH to TNS and other CNS structures involved with the migraine process providing enhanced feedback attenuation of clinical symptoms. The CNS and skin are both derived from the same embryological tissue (neuroectoderm), accounting for the rich neural connections between these two areas.

From the viewpoint of mechanism, TRNA may be seen as a combination of VNS and botulinum toxin (Botox) injection. TRNA is similar to VNS in functioning through afferent neural activation. Like Botox injection, TRNA drug action takes place at the peripheral

neural synapse. However, in contrast to VNS where surgical isolation of the vagus nerve at the anterior neck is required for direct afferent stimulation, cutaneous free nerve-endings below the skin surface at BONATH are utilized in TRNA for the same purpose. While Botox effect is at the neuro-muscular junction; in TRNA, it is at the sensory neuron receptor level.[8,9]

FIGURE 1



Cross-Section of the Skin

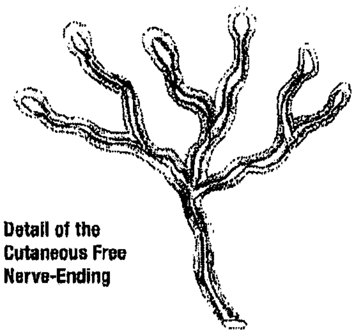
MIGRAINE: EXTENT OF THE PROBLEM & CURRENT TRIPTAN THERAPY

Despite significant advances in the understanding and treatment of migraine, a therapeutic void exists. Notwithstanding their efficacy and impact on migraine therapy, short-comings are apparent with triptans. Cost, tolerability, and overall acceptance contribute to the fact that much of the migraine population continues to rely on OTC products. Worldwide triptan use has not been as expected with seven same-class drugs on the market. The belief among some migraine sufferers is: considering the high cost of triptans, until the availability of something significantly more effective, safer, and convenient to justify change, OTC products are adequate. As migraine is not life-threatening but temporarily disabling, that logic seems difficult to argue.[1,8,10] Migraine headache affects some 28 million individuals in the US. The disorder is estimated to occur in 15% to 18% of women and 6% to 8% of men. Over 10% of the world population is afflicted by this medical condition. The World Health Organization (WHO) Task Force on Headache ranked migraine as one of the most disabling of chronic conditions; with attacks equating in disability to quadriplegia, psychosis, and dementia. Affected individuals are often young, productive, and in the prime of their lives; implying significant socio-economic impact.[11,12]

Introduced in the 1980s, triptans were developed to abort migraine attacks through their specific serotonin agonist action. They proved highly effective and significantly altered the approach to migraine treatment. With triptans, migraineurs were enabled to treat headaches without the need to see a doctor or go to the emergency room. Injections and treatments requiring healthcare professionals had been the usual practice for severe episodes. Patients were now capable of aborting attacks within a reasonably short (30 to 60 minutes) period of time and return to a relatively functional status. There was freedom to deal with migraine without the constraints of the healthcare delivery system.[7]

The success of triptans as a class was evidenced by six additional entries to market

FIGURE 2



Detail of the Cutaneous Free Nerve-Ending

after the first triptan, sumatriptan (Imitrex®): almotriptan (Axert®), frovatriptan (Frova®), zolmitriptan (Zomig®), naratriptan (Amerge®), rizatriptan (Maxalt®), and eletriptan (Relpax®). Sumatriptan is currently available as a tablet or in combination with the NSAID naprosyn (Treximet®), nasal spray, and subcutaneous injection. The other triptans are tablets except zolmitriptan, which also comes as nasal spray. Rizatriptan and zolmitriptan are available as plain or orally dissolvable tablets (ODTs).[1,13,14]

WHAT MIGRAINEURS WANT

In repeated surveys of migraine patients, rapid pain and symptom relief leads desire from therapy; followed by absence of recurrence, tolerability, convenience, and cost. The sumatriptan injection, although relatively rapid in onset, is associated with a higher incidence of side-effects and recurrence from drug bolus effect. The systemic and cerebral triptan effects of chest tightness, tingling of the face and extremities, lethargy, mental clouding, and fatigue are accentuated. Many also object to feeling a rush with the injection. Injections are considered invasive and viewed as inconvenient. Nasal spray is also generally not a preferred treatment for migraine. It may be associated with an objectionable taste as drug drips down the back of the throat.[10,15,16]

The pill is the most used form of triptan. However, the oral route may not be the most appropriate considering the clinical and pathological peculiarities of migraine. In addition to prominent head pain, significant gastrointestinal (GI) symptoms may occur during a migraine attack: nausea, vomiting, diarrhea, indigestion, and bloating. Patients are reluctant to take an oral drug when experiencing significant nausea and vomiting. Further, when vomiting occurs after pill ingestion, the question of repeating a dose arises. GI transit is impaired during the migraine process, delaying absorption of oral drugs. Studies also indicate absorption of oral triptans may be delayed by the presence of food in the digestive tract. Some orally ingested triptans are significantly metabolized by hepatic first-pass, affecting eventual drug blood levels. In the case of sumatriptan (Imitrex), nearly 85% of an oral dose is lost through hepatic first-pass metabolism.[17]

THE PROBLEM WITH SYSTEMIC DELIVERY OF TRIPTANS

All current triptan delivery relies on eventual presence in systemic and cerebral blood for therapeutic effect. Side effects are related to their presence in the circulation. Symptoms of chest tightness and numbness and tingling of the lips and extremities may be confused with those associated with more serious heart disease. This is further complicated by the fact that triptans have been demonstrated to cause vasocontriction. As a class, they are contraindicated with coronary artery disease, Prinzmetal's angina, and uncontrolled hypertension. They are likewise not advised in complicated migraine varients, such as hemiplegic and basilar migraine as these sub-types are associated with cerebrovascular vasocontriction and potential for stroke.[15-17]

The opinion of some headache experts is that overall triptan use has been limited by the potential for adverse events. Physicians are particularly reluctant to prescribe this drug class to older patients. Cardiac clearance may be recommended for such individuals prior to triptan use.[15,16]

IMPROVING TRIPTAN EFFECTIVENESS

In consideration of current limitations in triptan therapy, measures have been taken to enhance therapeutic benefit and widen use. To improve effectiveness of the plain sumatriptan tablet, it has been combined with the non-steroidal anti-inflammatory agent (NSAID), naprosyn (Treximet, GSK). NSAIDs are thought to block TNS synaptic central transmission. As non-selective cyclo-oxygenase (COX) inhibitors, the synthesis of prostaglandin, essential in the inflammatory component of migraine, is thought to be prevented.[1]

Studies are also underway with a transdermal sumatriptan patch (NuPathe) in an effort to maintain prolonged therapeutic blood levels of drug. However, with sustained triptan blood levels, issues with side effects and tolerability remain.[18]

THE UNIQUE MECHANISM OF TRNA TRIPTAN THERAPY

The author has applied triptans (eg, sumatriptan/Imitrex and frovatriptan/Frova), which are formulated as cream (12.5 mg sumatriptan in 0.5 ml) compounded in a dermal penetration-enhancing medium, to the BONATH of human patients. Through direct

effect on serotonin receptors of cutaneous free nerve-endings, afferent neural input is provided to TNS, effectively aborting the migraine process. As drug effect is achieved through neural connections than by bloodstream; clinical benefit is realized rapidly (10 to 15 minutes) and without the usual side effects of triptans.[19-21]

All current triptan delivery, whether injection, oral, nasal spray, or transdermal patch, ultimately require active drug in blood, exposing patients to side effects and other potential complications of systemic triptan therapy.[15,18]

TRNA DIFFERS FROM THE TRANSDERMAL PATCH

Although both are applied to the skin, TRNA triptan therapy differs from the systemic transdermal patch in that topically applied TRNA drug need only traverse the stratum corneum of the skin to reach cutaneous free nerve-endings for therapeutic effect. In contrast, the transdermal patch requires a drug concentration gradient for active drug to enter blood vessels in the subcutaneous tissue and dermis. These are at relative greater distance from the skin surface than the free nerve-endings (Figure 1). Further, after entry into the bloodstream, drug is required to be transported to the brain through cardiac output. As active drug is found in both systemic and cerebral blood, drug effect is not isolated to areas of migraine pathology, and extraneous effects are encountered. In contrast, in TRNA therapy, specific TNS pathways are affected through afferent neural connections from cutaneous free nerve-endings and upper cervical nerve roots. As therapeutic response is determined by rate of neural impulse than blood flow, clinical benefit is realized more rapidly with TRNA triptan delivery.[5,6]

TABLE 1

TRNA Versus Systemic Delivery (oral, injection, transdermal patch)

TRNA	Systemic
Direct affect on CNS through free nerve - endings and peripheral nerve connections.	Relies on therapeutic drug blood levels at CNS target sites.
Not rely on dermal, systemic, or cerebral blood flow for effect.	Drug enters systemic blood for effect after delivery by injection, patch, or as pill.
Rapid and prolonged drug effect as regional administration allows high tissue saturation of drug.	Therapeutic effect dependent on GI absorption, hepatic first pass, cardiac output, and cerebral blood flow.
Side - effects minimized without drug in systemic and cerebral blood.	Prone to systemic and CNS side effects.
Drug - drug interactions and metabolism/excretion negligible: may be considered "green."	Interactions with concomitant drugs and issues of metabolism and excretion.
Mechanism: analogous to electrical capacitor with charge build - up and discharge.	Mechanism: diffusion across concentration gradients and analogous to filling a reservoir to achieve a therapeutic level — fluid dynamics.

The analogy is of an electrical capacitor discharging after charge build-up (TRNA) compared to a fluid reservoir filling to a required therapeutic level (transdermal patch). Finally, with TRNA therapy, the specific placement of active drug, as acute use single-dose cream or sustained delivery patch, at the BONATH is key in capitalizing on the unique relationship of the region to TNS with respect to providing important afferent input. On the other hand, the systemic transdermal patch may be placed anywhere on the body as anatomical location is irrelevant to its mechanism of action. As dilution in blood is not a consideration with topical regional delivery, active drug dose requirements are also much lower (Table 1).[18]

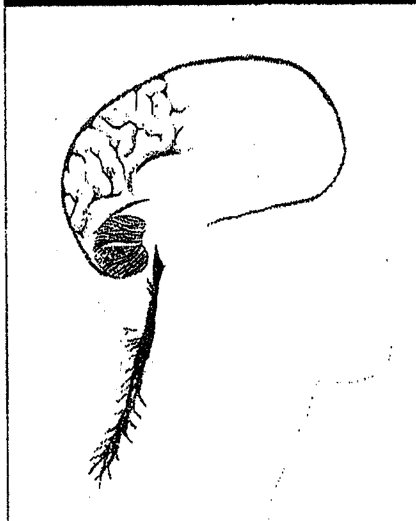
As alluded, the principles of TRNA therapy may also be applied to a sustained release patch and other depot drug delivery systems administered to the BONATH, with the only requirement of availing active drug to the cutaneous free nerve-endings for therapeutic effect. Conditions characterized by persistent, recurrent headaches, such as menstrual migraine, would benefit from such applications.

TRNA technology may be considered environmentally friendly or green. With negligible to no active drug in blood, there is lack of metabolism and excretion into the environment. Likewise, there is no concern for drug-drug interactions with concomitant medications.

CLINICAL EXPERIENCE WITH TRNA TRIPTAN THERAPY

In the 8 years of development, sumatriptan and tizanidine TRNA therapy has been used in over 300 patients, leading to the publication of five papers at

FIGURE 3



Trigemino-Cervical Complex: The Neuroanatomical Basis of Migraine

International Headache and Clinical Research Meetings. Observations with TRNA in established migraineurs with prior traditional triptan use indicated onset of relief of headache and other migraine symptoms occurred in the majority within 10 minutes of topical sumatriptan (12.5 mg sumatriptan) compounded cream application. Headache response (moderate/severe to mild/none) was achieved in the majority within 30 minutes; less than 10 minutes in 30%. No significant side effects, in particular triptan effects, were noted.[19-21]

Topical tizanidine (Zanaflex) alone or in combination with sumatriptan has also been investigated with TRNA technology in both migraine and tension-type headache with similar positive results. Studies are currently underway to evaluate the utility of this novel delivery process with other CNS-active drugs. The dopamine agonist apomorphine is being studied in Parkinson's disease and essential tremor with initial findings of significant clinical response to TRNA therapy.[22-24]

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BIOGRAPHY

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Exhibit D

Cervicogenic Headache: Anatomic Basis and Pathophysiologic Mechanisms

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Current Pain and Headache Reports 2001, 5:382–386
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Cervicogenic headache is pain perceived in the head but referred from a primary source in the cervical spine. The physiologic basis for this pain is convergence between trigeminal afferents and afferents from the upper three cervical spinal nerves. The possible sources of cervicogenic headache lie in the structures innervated by the C1 to C3 spinal nerves, and include the upper cervical synovial joints, the upper cervical muscles, the C2-3 disc, the vertebral and internal carotid arteries, and the dura mater of the upper spinal cord and posterior cranial fossa. Experiments in normal volunteers have established that the cervical muscles and joints can be sources of headache.

Introduction

Neurologists have strongly disputed what the defining clinical features of cervicogenic headache are. This entity, however, cannot be validly defined using conventional clinical criteria, such as those that apply to migraine or cluster headache. Cervicogenic headache shares too many features in common with other forms of headache for it to be defined in terms of the location of pain, its quality, periodicity, or associated features [1,2].

The singular defining criterion for cervicogenic headache is that it is pain perceived in the head but whose source lies in the cervical spine. The diagnosis of cervicogenic headache, therefore, relies on establishing a source of pain in the neck, using reliable and valid diagnostic techniques.

Physiologic Basis

The pathophysiology of cervicogenic headache has not been explicitly demonstrated. However, there is sufficient circumstantial evidence that the fundamental mechanism must be convergence. When primary afferents from two topographically separate regions of the body converge on the same second-order neuron in the spinal cord, nociceptive activity along one of the afferents can be perceived as pain arising in the territory of the other afferent.

In the context of cervicogenic headache, the convergence must be between nerves that innervate the head and nerves that innervate the cervical spine. This is not simply a matter of convergence between trigeminal and cervical afferents, for the head is innervated not only by the trigeminal nerve but also by cervical nerves. The occiput and regions as far forward as the coronal suture are innervated by the greater occipital nerve, the lesser occipital nerve, and the greater auricular nerve. Consequently, cervicogenic headache perceived in the forehead or orbital region requires convergence between trigeminal and cervical afferents, whereas cervicogenic headache perceived in the occiput requires convergence between certain cervical and other cervical afferents.

Anatomic studies in laboratory animals have revealed that the central terminals of the upper three cervical nerves overlap extensively [3,4]. In particular, the C2 spinal nerve not only ramifies in the grey matter of the C2 spinal cord segment but also sends ascending collaterals to the C1 segment, and descending collaterals to the C3 segment. The C3 spinal nerves express an analogous pattern of ascending and descending collaterals. The terminals of the C1 spinal nerve, however, are restricted to their own segment. This overlapping distribution of terminals allows for convergence between afferents from C1 and C2, and C2 and C3. Additionally, the spinal tract of the trigeminal nerve descends past the C1 and C2 segments, to end opposite at least to the C3 segment and perhaps as far caudally as the C4 segment [5,6]. From the tract, terminals of trigeminal nociceptive afferents ramify in the grey matter of the C1 to C3 spinal cord segments. This pattern of distribution allows for convergence between trigeminal afferents and afferents from any of the upper three cervical spinal nerves, and perhaps even the fourth.

Physiologic studies in laboratory animals have explicitly demonstrated convergence between trigeminal and cervical afferents. Neurons in the spinal cord can be found that respond to electrical stimulation both of the trigeminal nerve and of the cervical nerves. An earlier study showed convergence between the trigeminal nerve and afferents in the C1 dorsal roots [7]. A more recent study showed convergence between afferents from the superior sagittal sinus and afferents in the greater occipital nerve [8].

Exhibit E

P2-K16

Migraineurs' preference for sumatriptan over non-triptan therapy in a managed care population

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Background Numerous previous studies have validated the utility of triptan therapy in migraine management.

Objectives This study afforded migraineurs the opportunity to switch from non-specific therapy to sumatriptan 50 mg tablets. Resource utilization, patient satisfaction, and patient preference before and after access to sumatriptan and headache relief with sumatriptan were assessed.

Study design and patient enrolment This was an open-label, observational study conducted at two neurology offices in California. Study design utilized historical baseline data and a 3-month prospective treatment period. Thirty-one adults meeting IHS diagnostic criteria for migraine who were not using triptan medications as first-line therapy for migraines were enrolled.

Intervention and outcome assessment Subjects completed baseline and exit resource utilization and satisfaction questionnaires. Subjects were provided with sumatriptan 50 mg tablets and instructed to initiate treatment of migraine at the earliest onset of headache pain. Headache diaries, reviewed at an interim visit for completeness, captured time to meaningful relief, recurrence, and rescue medication use for each headache.

Results Twenty-nine evaluable patients treated 250 migraines. At baseline, subjects reported that the primary reason for not using migraine-specific triptan medications over conventional therapy was that a triptan was never prescribed (66%). At baseline, the most common non-triptans used to treat migraines included NSAIDs and other simple analgesics (69%), OTC or prescription combinations (28%), and narcotics (10%). At baseline, the majority of subjects reported dissatisfaction with current migraine therapy (76%). Summary of diary data showed that 164/250 (67%) of headaches was relieved with sumatriptan 50 mg tablets. 69% of patients preferred sumatriptan therapy over their previous non-triptan therapy, 16% preferred their previous therapy, and 14% had no preference. Primary reasons for preference for migraine-specific therapy included speed of relief (69%), effectiveness (30%) and lack of drowsiness (1%). Unscheduled MD visits went from 45 in the 3-month baseline period to 27 during the 3-month study period. ER visits went from 17 to 6, and hospitalizations went from 3 to 0.

Conclusion Most subjects preferred Sumatriptan 50 mg for first-line migraine therapy to previous non-triptan medications. Access to migraine-specific therapy enhances patients' satisfaction with managing their headaches.

P2-K17 #?

Transdermal sumatriptan: effectiveness and convenience in migraineurs

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Introduction Injectable sumatriptan revolutionized migraine therapy as a disease-process-specific measure for aborting migraine attacks. Nasal spray and oral forms of sumatriptan followed. Other oral triptans further increased treatment options. However, drawbacks with these agents exist. Injectable and nasal spray forms are inconvenient or undesirable with some patients. Oral triptans are problematic with significant nausea and gastrointestinal symptoms.

Purpose The efficacy of topical sumatriptan was studied over a six-week period in 22 migraineurs currently treating with injectable, nasal spray or oral sumatriptan. Migraine frequency for which triptan therapy was used ranged from 1 to >4 per week. Use of presently available triptan formulations had been established in these patients for several years. The purpose of the study was to determine the effectiveness and convenience of topical sumatriptan and to obtain an indication of preference for this method of administration in comparison to previous formulations.

Methods Commercially available sumatriptan tablets were crushed and compounded in a proprietary formula to give a concentration of 100 mg/mL. Patients were instructed to apply 50 mg of sumatriptan to a clean area of the forehead on the side of the headache at a time they would usually resort to using sumatriptan for relief. An additional 50 mg dose could be applied after 1 h if the first dose was ineffective. Application of the sumatriptan cream took about three seconds by placing it on the finger and rubbing the forehead several times.

Results To date, 11 patients that have used transdermal sumatriptan have responded. 6/11 (55%) reported transdermal sumatriptan relieved their headache. 4/11 (36%) indicated preference for the transdermal route and gave the following reasons: worked quickly (3); more convenient (4); and lack of side-effects (3). 4/11 (36%) achieved relief with a single 50 mg dose and time to relief was 10 min (1), 30 min (1) and 60–120 min (1); one patient did not indicate. 2/11 patients preferred injectable sumatriptan; 2/11 preferred nasal spray. None indicated specific preference for the pill.

Discussion These preliminary findings suggest that topically applied sumatriptan may be a viable option for management of acute migraine. The lack of need for GI absorption and diminished 'first pass' component to the liver may account for a more rapid effect and less side-effects. Additional studies may include a double-blind placebo crossover protocol; assessing sumatriptan blood levels after topical administration; the use of pure sumatriptan rather than pills; and a sustained delivery system for menstrual migraine.

TRANSDERMAL SUMATRIPTAN:
Effectiveness and Convenience in Migraineurs

Ronald Aung-Din, M.D., Michelle Malatian, Pharm.D. and Michael Pass, R.Ph., F.I.A.C.P.

INTRODUCTION

- Injectable sumatriptan revolutionized migraine therapy as a disease-process-specific measure for aborting migraine attacks, followed by nasal spray and oral formulations.
- However, injectable and nasal spray formulations may be considered inconvenient or undesirable by some patients and oral formulations can be problematic if the patient experiences significant nausea and gastrointestinal symptoms.

OBJECTIVES

The objectives of the study were to determine the effectiveness and convenience of topical sumatriptan and to obtain an indication of the preference for topical administration compared to previous formulations.

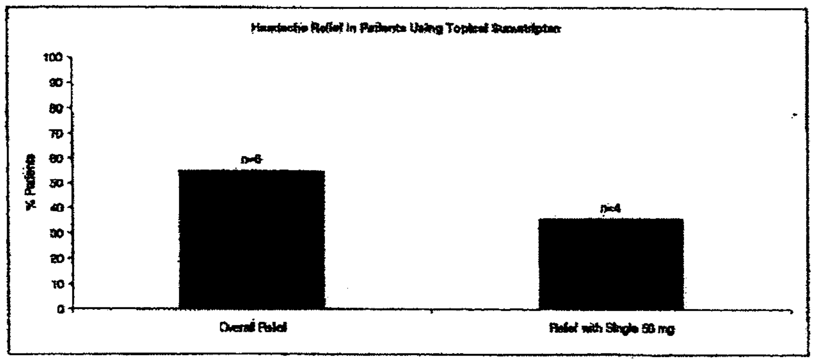
METHODS

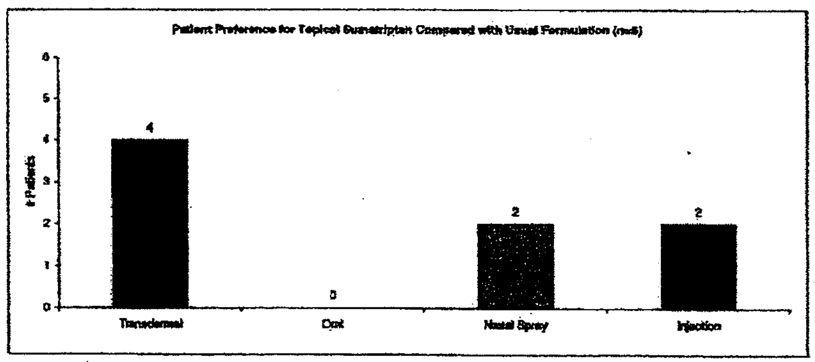
Subjects

- 22 adult migraineurs currently using sumatriptan subcutaneous injection, nasal spray, or tablets.
- Migraine frequency ranged from 1 to >4 per week.
- All patients have used currently available triptan formulations for years.
- Patients used topical sumatriptan to treat their migraines over a 6 week period.

Topical Sumatriptan

- Commercially available sumatriptan tablets were compounded in a proprietary formula to give a concentration of 100 mg/ml.
- Patients were instructed to apply 50 mg of sumatriptan to a clean area of the forehead on the same side as the headache pain at the time they would use sumatriptan.
- An additional 50 mg dose could be applied after one hour if the first dose did not completely relieve headache pain.
- Application of the sumatriptan cream took about three seconds by placing it on the finger and rubbing the forehead several times.





RESULTS

- To date, 11 patients that have used transdermal sumatriptan have responded.
- 6/11 (55%) reported transdermal sumatriptan relieved their headache.
- 4/11 (36%) indicated preference for the transdermal route and gave the following reasons: worked quickly (n=3); more convenient (n=4); lack of side effects (n=3).
- 4/11 (36%) achieved relief with a single 50 mg dose and time to relief was ten minutes (n=1), 30 minutes (n=1) and 60-120 minutes (n=1); one patient did not indicate time to relief.
- 2/11 patients preferred sumatriptan subcutaneous injection; 2/11 preferred nasal spray. None indicated preference for the tablet.
- Transdermal sumatriptan was well tolerated.

CONCLUSIONS

- These preliminary findings suggest that topically applied sumatriptan may be a useful alternative to traditional sumatriptan formulations for management of acute migraine.
- The lack of need for GI absorption and diminished "first pass" component to the liver may account for a more rapid effect and less side effects.
- Double-blind, placebo controlled studies are warranted to confirm these findings.
- Additionally, sumatriptan blood concentrations after topical administration should be assessed; the use of crystalline sumatriptan rather than crushed tablets should be evaluated; and a sustained delivery system for prophylaxis for menstrual migraine should be considered.

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Exhibit F

aura (n=95), 83% in those who usually have aura associated with migraine (n=42), and 85% in those who normally have migraine duration less than 12 hours (n=52). Analysis from study B showed that 2-hour pain-free rates were highest in patients with headaches of mild baseline intensity (71% to 79%), followed by those with moderate (52% to 58%) or severe (32% to 38%) baseline intensity. Patient satisfaction with zolmitriptan 5 mg nasal spray was rated as good or excellent by 58% of patients in study A and 70% of patients in the 12 month studies (B and C). Patients who had a poor or fair response to previous triptan therapy reported good (52%) or excellent (57%) response to zolmitriptan nasal spray, respectively (Study A).

Conclusions: Zolmitriptan 5 mg nasal spray was highly efficacious across various subpopulations of migraine patients, especially in those representing typical migraine patients commonly seen in clinical practice. Furthermore, patients were highly satisfied with zolmitriptan nasal spray treatment in both the long and short term studies. Together with the very fast onset of action, these results demonstrated in previous trials, suggest that zolmitriptan 5 mg nasal spray offers significant benefits for patients with migraine. (1) Becker WJ, Lee D. Zolmitriptan nasal spray is effective, fast acting and well tolerated during both short and long term treatment. Cephalalgia 2001;21:271.

F13 [redacted]

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Objectives: The current trial investigated the effectiveness of transdermal migraine therapy with sumatriptan extracted from tablets and solubilized in Lipoderm® using a proprietary method at a dose of 12.5 mg sumatriptan. This open-label study also sought to determine the tolerability of this mode of acute migraine treatment in a "real life" setting.

Background: Two previous trials utilizing sumatriptan showed promising results as a transdermal treatment of acute migraine. In these studies, crushed sumatriptan tablets in microemulsion in pluronic lecithin organogel (PLO) and Lipoderm® were respectively formulated to doses of 50 mg and 100 mg sumatriptan.

Methods: Forty-two patients presenting to an outpatient clinic over a 6-week period with acute moderate-to-severe migraine were [redacted] extracted [redacted] in Lipoderm®. Two patients presented twice during the study period. The [redacted]

Results: The 12.5 mg dose of transdermal sumatriptan was effective in decreasing headache pain and associated migraine symptoms of cervical muscle tension, nausea, vomiting and photophobia in all treated patients. [redacted] of sumatriptan gel application. [redacted] Three [redacted] patients with persistent moderate headache pain at 30 minutes responded after redosing. Headache recurred in three patients. Five patients (11%) experienced side effects of slight light-headedness, dizziness, or throat/tongue tingling. There were no side effects of chest tightness or chest pain.

Conclusions: Upon topical application, the sumatriptan gel (12.5 mg in Lipoderm®) provided rapid, well-tolerated migraine headache pain and symptom relief. The majority of treated [redacted] patients noted [redacted]

sign of migraine relief. This, together with the rapid headache [redacted] relief, suggests a [redacted] convergence of [redacted] Further studies, including placebo-controlled design, are necessary to clarify these and other issues with this novel dosage form of acute migraine therapy. Transdermal triptan therapy is potentially useful as an alternative to existing treatment options.

F14
Valdecoxib Effectively Treats a Single Moderate or Severe Acute Migraine Headache

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Objectives: Primary: Demonstrate superior analgesic efficacy of single 20- & 40-mg doses of valdecoxib vs placebo (PBO) in treatment of a single moderate or severe acute migraine headache (HA). Secondary: Evaluate other efficacy factors, tolerability, and safety of valdecoxib vs PBO.

Background: Valdecoxib (V), an oral COX-2 specific inhibitor, is indicated for relief of signs & symptoms of rheumatoid arthritis & osteoarthritis & treatment of primary dysmenorrhea. The optimal dose of V for treatment of migraine HA is assessed in this study.

Methods: Double-blind, randomized, PBO- & active-controlled, multicenter, single and multiple-dose, 56-day study of V in treatment of a single, acute, IHS-diagnosed moderate or severe migraine HA, with or without aura. Patients assessed HA pain intensity (HPI) (0 = none, 1 = mild, 2 = moderate, 3 = severe) & presence or absence of migraine-associated nausea (N), vomiting (VM), phonophobia (PN), and photophobia (PT) at intervals from 0-24 h postdose (PD). The primary efficacy endpoint was the HA response rate (R; % of patients with HPI reduced from severe/ moderate to mild/none) 2-h PD. Sumatriptan (S) 50 mg (encapsulated to maintain blinding) was included as an active control for assay sensitivity. Adverse events (AE) and safety parameters were monitored throughout the study.

R and Frequency of migraine-associated symptoms at 2-hr PD, % of patients

	PBO	V 20 mg	V 40 mg	S 50 mg
R	29.8	43.2***	48.3***	62.0**
N	51.1	40.0*	29.1***	44.8*
VM	7.1	0.7***	2.0**	5.6*
PN	53.9	51.9*	41.7**	46.2*
PT	69.5	65.2*	58.5*	58.7*

*$p \geq 0.05$ vs PBO
**$p \leq 0.05$ vs PBO
***$p \leq 0.025$ vs PBO

Results: 570 patients (135 V 20 mg, 151 V 40 mg, 141 PBO, 143 S) comprised the ITT population, with no significant differences in baseline demographics between treatment groups. The 2-h R with V 20 mg, V 40 mg, and S 50 mg was significantly improved compared with PBO (Table). R with V 40 mg was significantly greater than that with PBO ($p \leq 0.025$) at all time points from 2-24 h, as was R with S 50 mg ($p \leq 0.05$). R with V 20 mg was significantly greater than PBO ($p \leq 0.05$) from 2-4 h. Significantly fewer patients treated with V 40 mg, compared with PBO, experienced N, VM and PN at 2 h PD (Table). From 3-24 h, V 40 mg was significantly superior to PBO for N, PT, and PN ($p \leq 0.025$ for each). V 20 mg was more effective than PBO in reducing the frequency of VM at 2, 3, and 4 h PD ($p < 0.05$). From 3-24 h PD, V 20 mg reduced the frequency of N & PT compared with PBO ($p \leq 0.025$, $p \leq 0.05$ respectively). For N,

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Transdermal Sumatriptan in Clinical Practice:
The Experience of 42 Patients with Acute Migraine in an Outpatient Setting

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INTRODUCTION

Seven triptans are currently available for abortive therapy of acute migraine. Except for sumatriptan and zolmitriptan, others are in oral form. Injection and nasal spray may be considered inconvenient or undesirable by some patients. "Melt" tablets still require gastrointestinal (GI) absorption. Nausea and vomiting are prominent symptoms of migraine. GI absorption of triptans can be delayed during the migraine process and by the presence of food in the GI tract. Thus, the prospect of triptan delivery that obviates GI absorption and bypasses hepatic "first pass" and systemic circulation requirements becomes attractive. Two previous open-label studies with sumatriptan as microemulsion in pluronic lecithin organogel (PLO) and Lipoderm® suggested promise for the transdermal treatment of migraine.

OBJECTIVES

The current trial investigated the effectiveness of transdermal migraine therapy with sumatriptan extracted from tablets and solubilized in Lipoderm® using a proprietary method at a dose of 12.5mg sumatriptan. This open-label study also sought to determine the tolerability of this mode of acute migraine treatment in a "real life" setting. The study population consisted of migraineurs presenting to an outpatient clinic over a 8-week period.

METHODS

Design

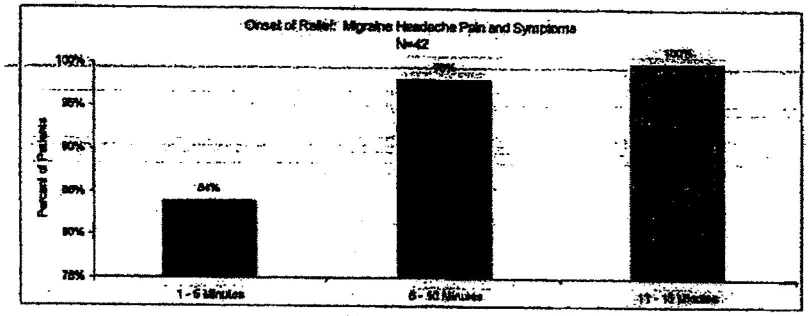
- Open-label, single-dose, prospective study (N=42)
- Subjects: Migraineurs (I.H.S. 1.1, 1.2 or 1.7) male & female with a history of prior triptan use in different formulations
- Migraine frequency was 1 to 4 per week
- Patients using opiod or barbiturate-containing medication 24 hours prior to administration of transdermal sumatriptan were excluded

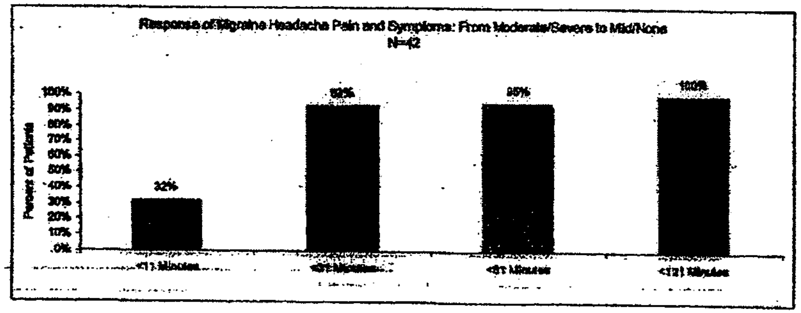
Treatment

- Patients were treated for one moderate-to-severe migraine headache with transdermal sumatriptan 12.5mg in Lipoderm® (0.1ml of 125mg/ml of extracted sumatriptan solubilized in Lipoderm®)
- The transdermal sumatriptan gel was applied to the mid-posterior cervical area at the hairline using a calibrated 0.5cc syringe and gently rubbed [illegible]
- Opiod or barbiturate containing medications also could not be administered for 24 hours following transdermal sumatriptan

Assessments

- Patient self-report of: (1) onset of relief of headache and migraine symptoms, (2) headache response (mild or no headache), (3) headache recurrence within 24 hours of treatment and (4) side effects





RESULTS

Demographics

- 38 females and 4 males participated in the study
- Mean age of participants: 43 years
- Mean duration of migraine headaches: 17 years
- 2 patients presented twice during the study period, resulting in a total of 44 patient encounters

Outcome

- 95% (42/44) treated patients reported 12.5mg of transdermal sumatriptan was effective in decreasing headache pain and associated migraine symptoms of cervical muscle tension, nausea/vomiting, and photophobia
- Onset of headache relief was apparent on average within 5 minutes (range 1-12 minutes) of sumatriptan gel application
- Headache response rates (mild or no headache) were [illegible] at 10 minutes and [illegible] at 30 minutes
- 3 patients with persistent moderate headache pain at 30 minutes responded after redosing with 12.5 mg transdermal sumatriptan
- 3 patients (7%) experienced headache recurrence within 24 hours of treatment with transdermal sumatriptan
- 5 patients (11%) experienced side effects of slight light-headedness, dizziness, or throat/tongue tingling. There were no side effects of chest tightness or chest pain.

CONCLUSIONS

- These findings suggest transdermal sumatriptan is effective and well tolerated in a "real life" outpatient clinical setting and may be potentially useful as an alternative to existing triptan treatment options
- This reformulated preparation using chemically extracted sumatriptan in Lipoderm® appeared to provide improved efficacy over the previous methods using crushed tablets in microemulsion
- Relaxation of cervical muscle tension was frequently the first sign of migraine relief. This suggests the possible operation of a "peripheral de-afferenting mechanism" aborting central migraine processes through nociceptive convergence of cervical afferent projections on trigeminal nuclei
- Further studies including placebo controlled design are necessary to clarify these and other issues with this novel dosage form of acute migraine therapy

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